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Safety and Efficacy of Cold-Adapted Influenza Vaccine (CAIV-T)

Advisory Committee on Immunization Practices
October 25, 2006

Presentation

- FluMist® product profile
- Milestones for CAIV-T development
- Safety and efficacy data to support expanded age indication

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FluMist®

- **Live attenuated vaccine**
- **Trivalent (A/H1N1, A/H3N2, B)**
- **Needle-free nasal mist administration**
  - Dose = 0.5ml (0.25ml /nostril)
  - Single annual dose for ≥ 9 through 49 years
  - Two doses for 5 through < 9 years if not previously vaccinated with FluMist
- **Thimerosal-free**
- **Stored frozen**

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FluMist®
Current Indication

Active immunization for the prevention of disease caused by influenza A and B in healthy individuals 5 to 49 years of age

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FluMist® Milestones
Frozen Formulation

- **June 2003:**
  - Approved
- **December 2005:**
  - New bulk manufacturing facility in U.K. approved
  - 90M trivalent bulk dose capacity
- **June 2006:**
  - Plasmid rescue for FluMist manufacturing approved
- **Lot release schedule 2006:**
  - First doses in July; all doses available before end of September

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Comparison of FluMist® and CAIV-T

	FluMist (Frozen Formulation)	CAIV-T (New Formulation)
Regulatory Status & Age Indication	Licensed in U.S. Healthy persons aged 5 – 49 years	Investigational (under review by FDA)
Storage	≤ -15º C Freezer	2-8º C Refrigerator
Excipients	SPG	SPG, arginine, hydrolyzed porcine gelatin
Preservatives	None	None
Dosage	0.5mL (0.25mL per nostril)	0.2mL (0.1mL per nostril)

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CAIV-T Regulatory Milestones

- **September 2005:**
  - sBLA filed for CAIV-T=FluMist®
- **July 2006:**
  - sBLA filed to expand label for children 12-59 months without history of asthma or wheezing
  - May 2007: PDUFA date - standard review process

Large Scale Efficacy Trials in Children

All matched culture-confirmed influenza

Placebo Controlled Studies				
Study	**Placebo**	**CAIV-T / FluMist**	**% Efficacy**	**95% CI**
D153-P501, Y1	12.5%	3.4%	73%[a.b.c]	(63, 81)
D153-P502, Y1	10.8%	1.6%	85%[a,c]	(74, 92)
AV006, Y1	18%	1%	93%[b,c]	(88, 97)
TIV Controlled Studies				
Study	**TIV**	**CAIV-T**	**% Reduction**	**95% CI**
D153-P514	4.8%	2.3%	53%[a,c]	(22, 72)
D153-P515	6.4%	4.1%	35%[c]	(4, 56)

Significant efficacy demonstrated vs. A/H1[a], A/H3[b], B[c]

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CP111 Pivotal Study Design

- **Randomized, double-blind, multinational study**
- **Active-control (TIV)**
- **Children 6 – 59 months of age (N = 8,475)**
  - All included except recent wheezing, severe asthma and immunocompromised
- **Primary endpoint: culture-confirmed modified CDC influenza-like illness (CDC ILI)**
  - An increased temperature (≥ 100ºF oral or equivalent) plus the presence of cough, sore throat or runny nose/nasal congestion occurring on the same or consecutive days

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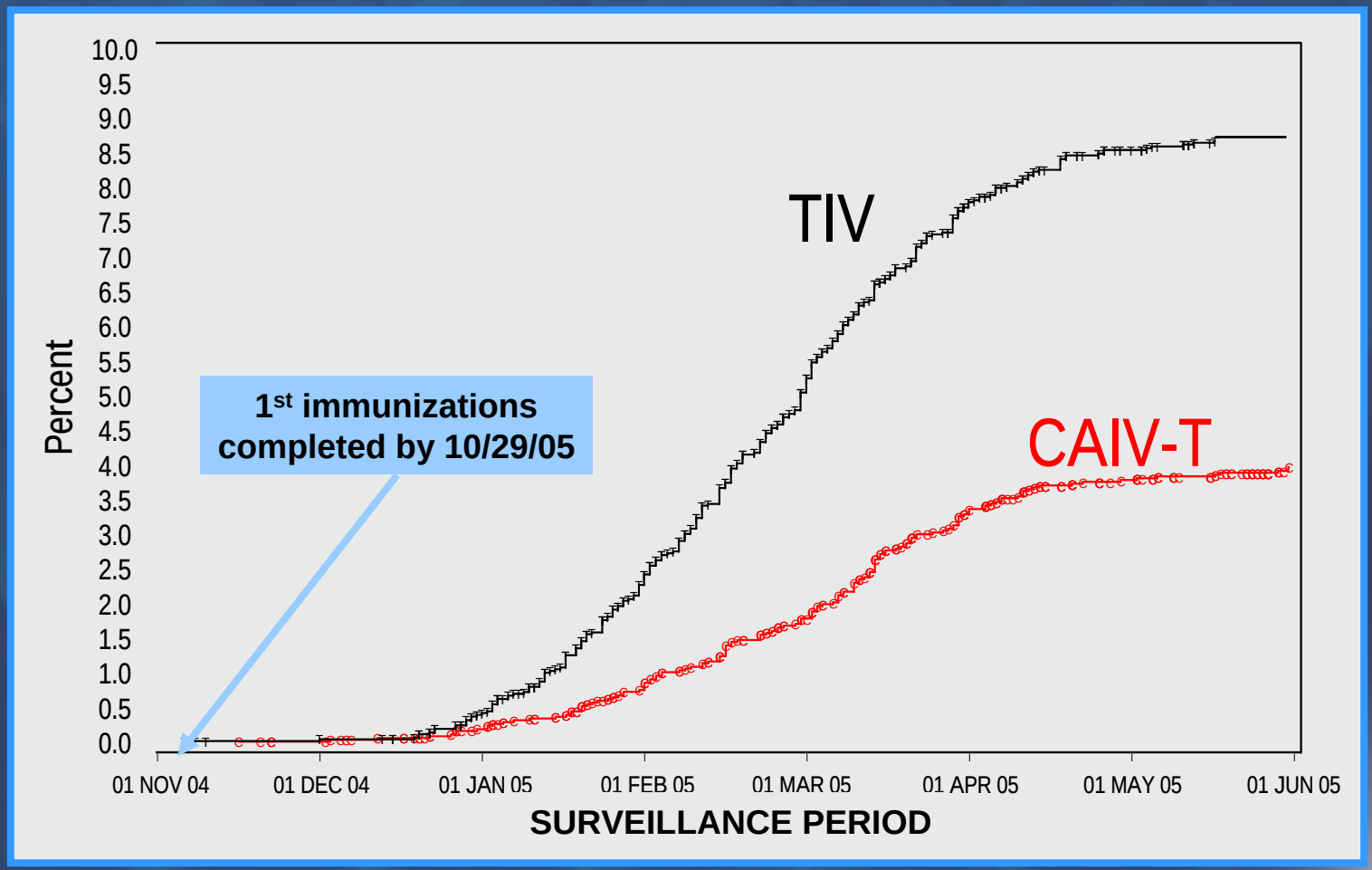
CP111 Reported Cases of Influenza

Culture-confirmed Modified CDC-ILI Influenza Caused by Any Wild-type Strain



According to Protocol (ATP) Population

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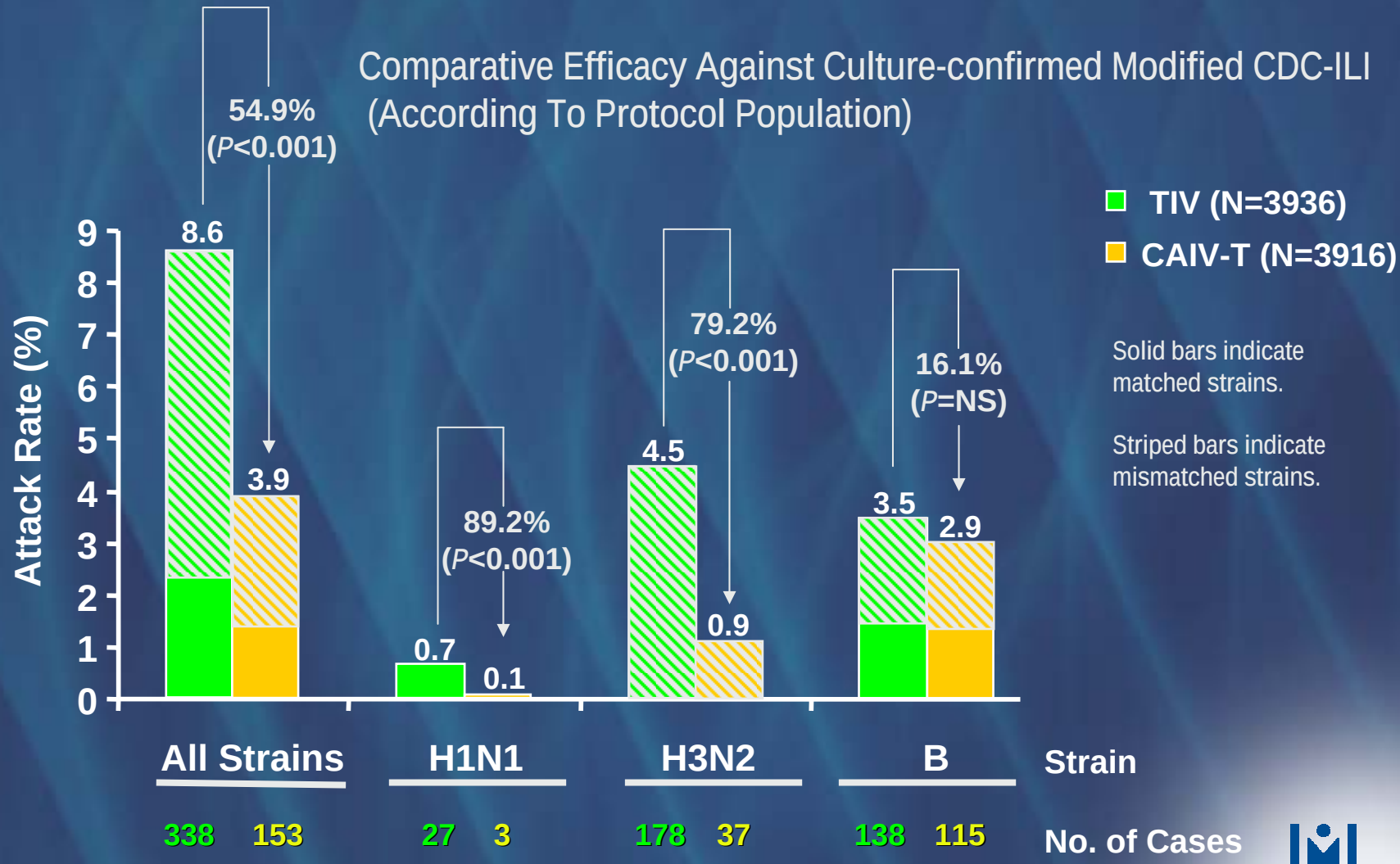
CP111 Efficacy Comparison



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CP111: Pre-Specified Safety Analyses
CAIV-T vs. TIV

- **Rates of SAEs were similar**
- **Rates of AEs were as expected**
  - CAIV-T ↑ runny/stuffy nose
  - TIV recipients ↑ injection site reactions
- **Medically significant wheezing**
  - Children <2 yrs (2 dose group), statistically significant increase in MSW within 42 days after dose 1
    - CAIV-T (N = 55, 3.2%), TIV (N = 34, 2.0%)
    - Weeks 2, 3, and 4 after immunization
    - Rates not statistically different after 42 days or after dose 2

CP111: MSW in Children <24 Months *Severity Similar for CAIV-T and TIV*

- **MSW-associated hospitalization**
  - Rates: 0.3% CAIV-T vs 0.2% TIV
  - Duration: median 4.5 days CAIV-T vs 4 days TIV
- **Deaths (none)**
- **ICU or ventilator use (none)**
- **Recurrent MSW rates**
  - ≥ 1 recurrence: CAIV-T 32% vs. TIV 28%
  - ≥ 2 recurrences: CAIV-T 2.6% vs. TIV 4.0%

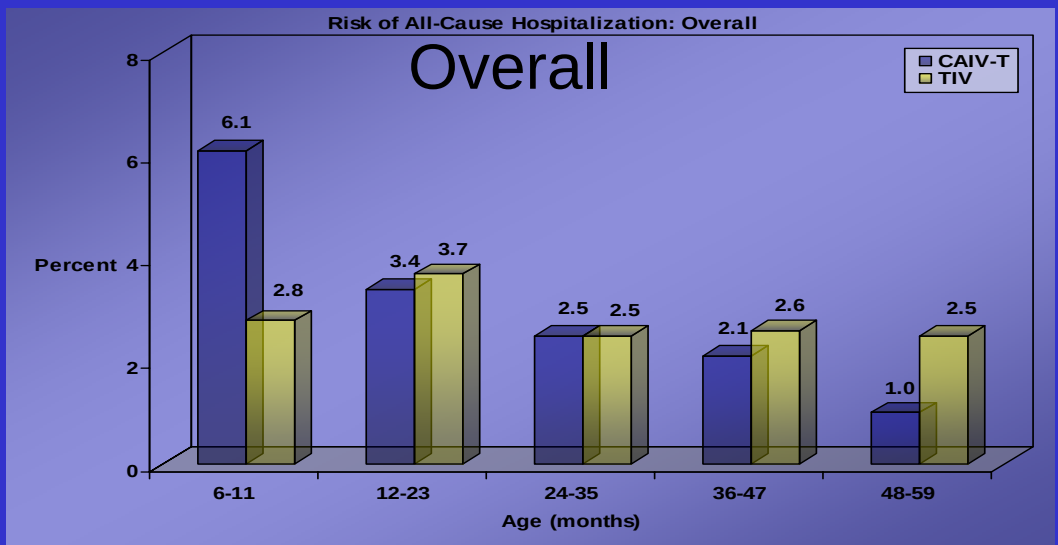
CP111 Post-Hoc Exploratory Analyses

- Medically significant wheezing (MSW) and hospitalization through the entire study
- Assessment of history of wheezing/asthma

CP111 Hospitalizations

Entire Study Period

- All cause hospitalization increased only in children 6-11 months of age



CAIV-T*	684	1,308	1,372	433	382
TIV*	683	1,292	1,379	460	359
p-value	0.003	0.706	0.920	0.601	0.130

* Numbers in table represent total subjects for each age and treatment group

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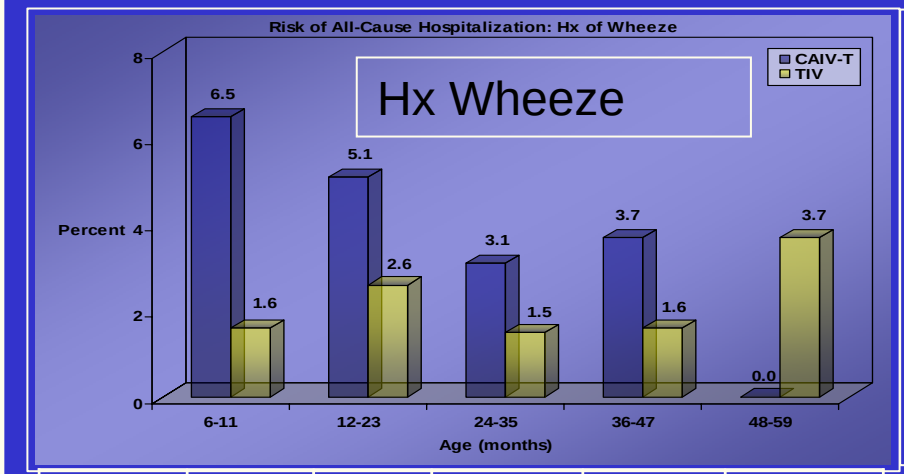
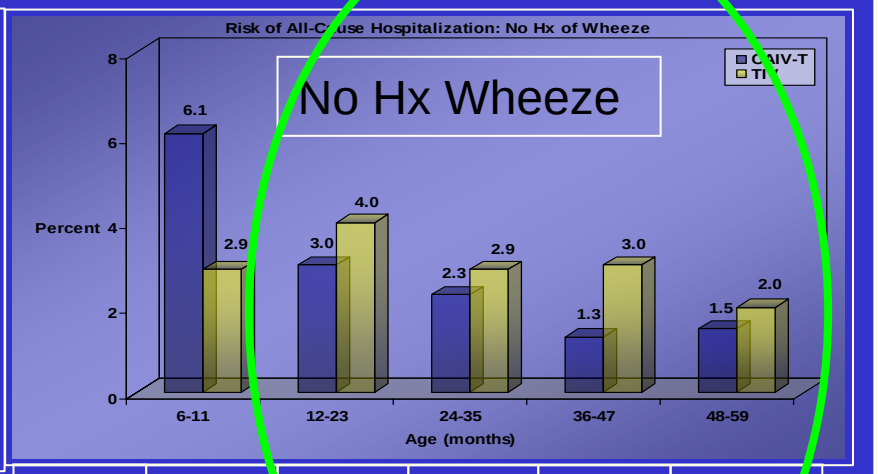
CP111 Hospitalizations

Entire Study Period

- Children in the CAIV-T group 12-47 months *with* a history of wheeze had higher rates of hospitalization
- No hospitalization risk was associated with CAIV-T in children 12-59 months *without* a history of wheeze



	6-11	12-23	24-35	36-47	48-59
CAIV-T*	77	254	321	136	111
TIV*	63	231	333	129	107
p-value	0.154	0.153	0.168	0.281	0.040



	6-11	12-23	24-35	36-47	48-59
CAIV-T*	607	1,054	1,051	297	271
TIV*	620	1,061	1,046	331	252
p-value	0.007	0.248	0.398	0.156	0.655

* Numbers in table represent total subjects for each age and treatment group

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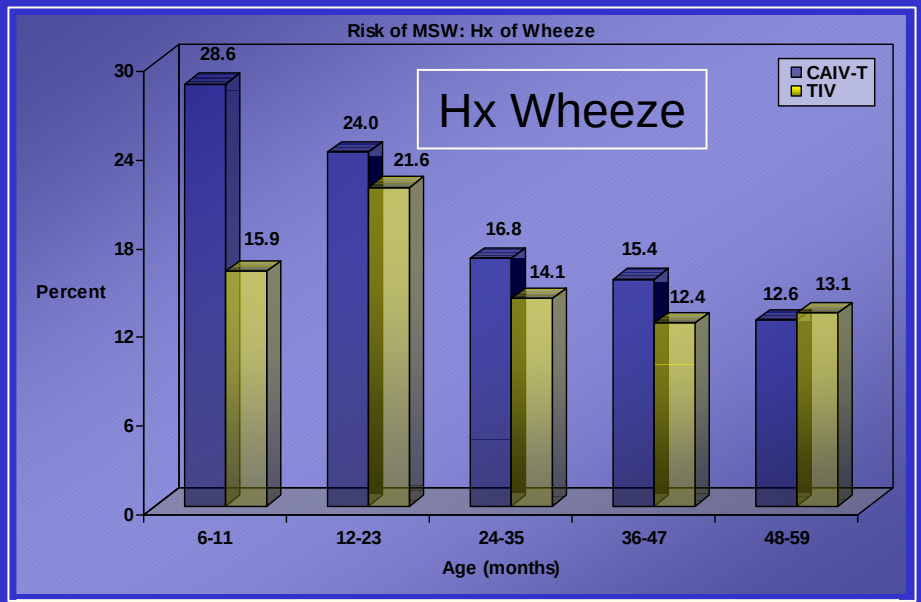
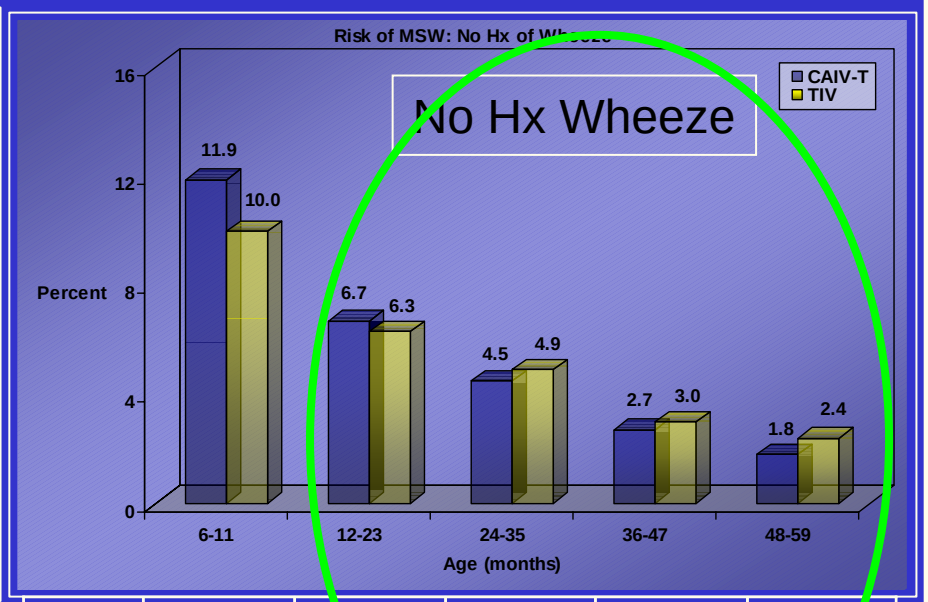
MSW Risk by History of Wheezing
Entire Study Period

- CAIV-T 12-47 months *with* a history of wheeze had higher rates of MSW



CAIV-T	77	254	321	136	111
TIV	63	231	333	129	107
p-value	0.075	0.535	0.338	0.476	0.917



CAIV-T	607	1,054	1,051	297	271
TIV	620	1,061	1,046	331	252
p-value	0.296	0.695	0.661	0.806	0.670

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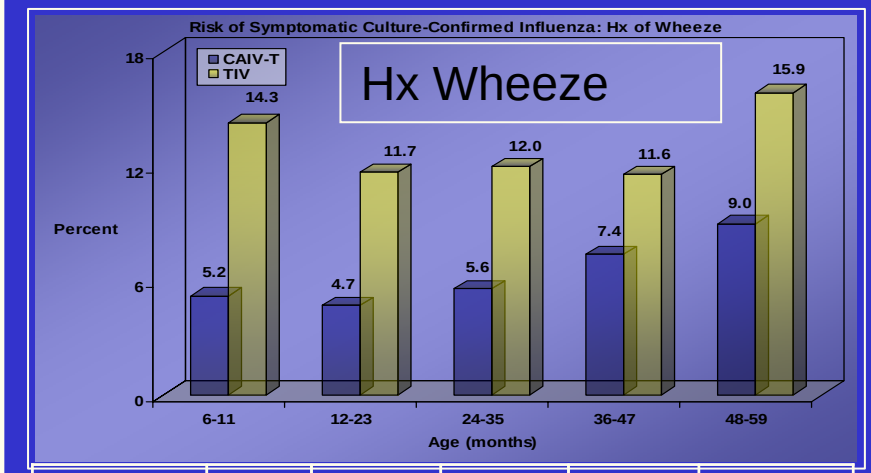
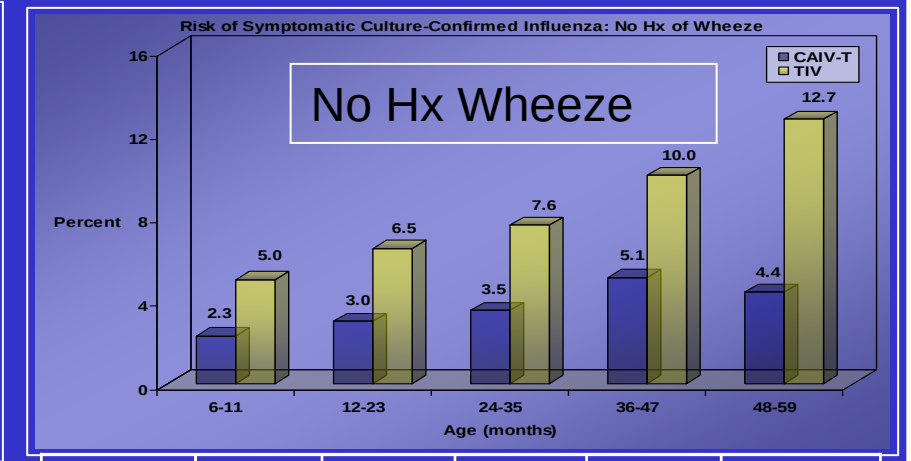
Reduction of Influenza Disease

- Benefit seen in all age groups of children with and without a history of wheezing



CAIV-T*	77	254	321	136	111
TIV*	63	231	333	129	107
p-value	0.065	0.005	0.004	0.234	0.123



CAIV-T*	607	1,054	1,051	297	271
TIV*	620	1,061	1,046	331	252
p-value	0.012	<0.001	<0.001	0.021	0.001

* Numbers in table represent total subjects for each age and treatment group

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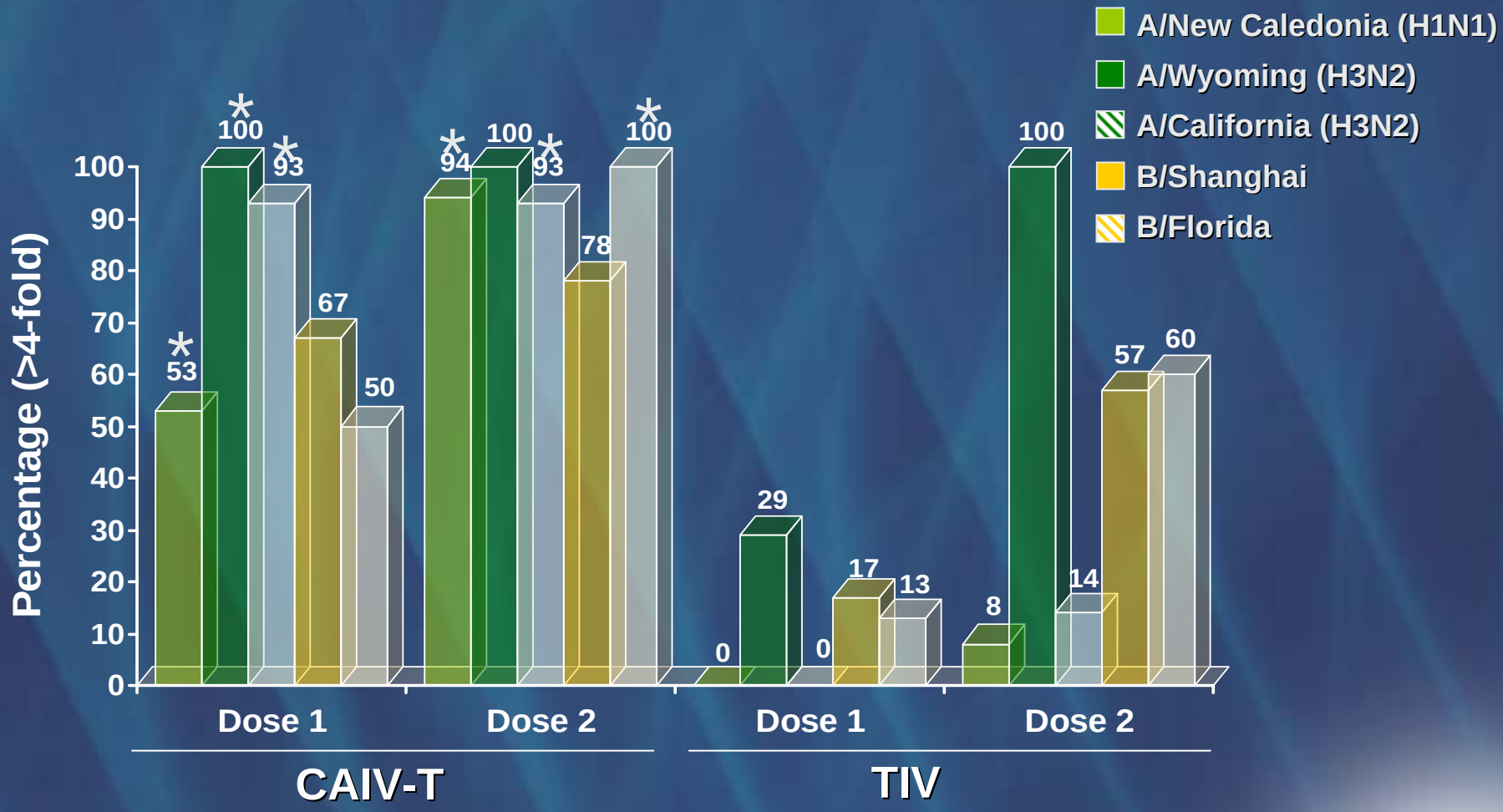
HAI Response in Seronegative Infants
Seroconversion Rates -CP123



* Statistically significant

Vaccine strains shown in solid bars
Drift strains shown in hatched bars

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Summary

- Superior efficacy against matched and mismatched influenza
- Safety of CAIV-T for children <12 months needs further evaluation
- May be higher rate of all-cause hospitalization in children with Hx of wheeze to age 47 months
- In children 12-59 months without Hx of wheeze, CAIV-T appears to have a *highly favorable* risk-benefit profile
- Children without a history of wheeze account for ~80% of all children between 12-59 months
- CAIV-T is currently under regulatory review

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